REMARKS

Status Summary

Entry of the Preliminary Amendment, which claims priority to the filing date of parent application U.S. Serial No. 09/259,338, is acknowledged. Claims 1-19 were examined. The specification and Figure 1 are objected to for informalities. Claims 1-19 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1-5, 8, 10-14, and 17-18 are rejected under 35 U.S.C. § 102(b) and/or 102(e)

A formal copy of Figure 1 is filed herewith in response to the Draftperson's review. The specification is amended to correct informalities. Claim 1 is amended and claim 19 is canceled. Attached hereto is a marked-up version of the changes made to the specification and to claim 1. The attached Appendix is captioned "Version With Markings To Show Changes Made." No new matter is added by the claim amendments. It is believed that the application is now in condition for allowance, and reconsideration of the application as amended is respectfully requested.

Objection to the Specification

The disclosure is objected to for incomplete reference to co-pending patent applications. Office Action, at page 2, ¶ 2-3. The specification is amended to properly identify U.S. Serial Nos. 09/259,337 and 09/259,347, which disclose methods for determining percent binding affinity and immunoreactivity of conjugates after labeling.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 1-19 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite based on recitation of "ligand" and "the radiolabelled antibody." Office Action, at page 2, ¶ 4-6. Claim 1 is amended to provide proper antecedent basis for each recited element and is believed to comply with the requirements of 35 U.S.C. § 112, second paragraph. Claims 2-19 ultimately depend from claim 1 and are also believed to comply with 35 U.S.C. § 112, second paragraph.

Claim 18 is also rejected under 35 U.S.C § 112, second paragraph, as allegedly indefinite based on recitation of "70%" binding specificity. The Examiner states that claim 18 is unclear as to what binding specificity is 100%. Office Action, at page 2, ¶ 7. This rejection is respectfully traversed. Applicant responds that the term "binding specificity" is understood in the art to represent the percentage of labeled antibody that binds to a target

antigen (*i.e.*, CD20) relative to binding of the same antibody to a non-specific antigen. The subject application uses the term "binding specificity" according to this art-recognized definition. For example, the application as originally filed describes performance of a binding assay using cells that express or do not express target antigen (page 22, line 9, through page 23, line 3). The binding results are expressed in Table 1 (page 24), Table 2 (page 25), and Table 3 (page 26). Thus, claim 18 is believed to particularly point out and distinctly claim the present invention in compliance with the requirements of 35 U.S.C. § 112, second paragraph.

Based on the foregoing, applicant respectfully requests that the rejection of claims under 35 U.S.C. § 112, second paragraph, be withdrawn. Allowance of claims 1-19 is also respectfully requested.

Rejection of Claims Under 35 U.S.C. § 102(b)

Based on Matheret al.

Claims 1-5, 8, 10-14, and 17-18 are rejected under 35 U.S.C. § 102(b) as assertedly anticipated by Mather et al. (1989) *Eur J Nucl Med* 15:307 ("Mather"). Office Action, at page 3, ¶ 3, through page 4, ¶ 2. Mather describes preparation of ^{90}Yttrium-labeled antibodies that can be administered to a patient in the absence of post-labeling purification. Although Mather recognizes radiolysis of the labeled antibodies that results in sub-optimal *in vivo* results, the Examiner contends that the properties of "sufficient purity, specific activity, and binding specificity" require quantitative values to distinguish the present invention over the prior art. This rejection is respectfully traversed.

Applicant notes that the radiolabeled antibodies prepared by Mather are of modest specific activity (1 mCi/mg), which are therefore largely inadequate for clinical use. Claim 1 is amended to recite a radiolabeled protein, ligand or peptide "having a specific activity of at least about 5 mCi/mg." Support for the claim amendment can be found in the subject application as originally filed, for example at page 13, line 11, through page 14, line 1 and in original claim 19 (now canceled). Based thereon, claim 1 is believed to be patentably distinguished over Mather. Claims 2-5, 8, 10-14, and 17-18 ultimately depend from claim 1 and are also believed to be patentably distinguished over Mather. Thus, applicant respectfully requests that the rejection of claims 1-5, 8, 10-14, and 17-18 under 35 U.S.C. § 102(b) based

on Mather be withdrawn. Allowance of claims 1-5, 8, 10-14, and 17-18 is also respectfully requested.

Rejection of Claims Under 35 U.S.C. § 102(b)

Based on Richardson et al.

Claims 1, 8, 10-14, and 17-18 are rejected under 35 U.S.C. § 102(b) as anticipated by Richardson et al. (1987) *Nucl Med Commun* 8:347 ("Richardson"), which describes radiolabeling of antibodies with ^{111}Indium. This rejection is respectfully traversed.

As noted in the application as originally filed, methods for radiolabeling antibodies for diagnostic applications are inadequate for preparation of therapeutic radioconjugates. In particular, prolonged duration of labeling reactions can cause significant radiolysis of an antibody or protein labeled with high energy radioisotopes suitable for therapeutic applications.

Claim 1 is amended to include the term "therapeutic" to describe "radioisotope" in step (i). As such, claim 1 is believed to be patentably distinguished over Richardson, which only describes preparation of radioconjugates useful for diagnosis. Claims 8, 10-14, and 17-18 ultimately depend from claim 1 and are also believed to be patentably distinguished over Richardson. Thus, applicant respectfully requests withdrawal of the rejection of claims 1, 8, 10-14, and 17-18 based on Richardson. Applicant also respectfully requests allowance of claims 1, 8, 10-14, and 17-18.

Rejection of Claims Under 35 U.S.C. § 102(b)

Based on Chinol et al. and Hnatowich et al.

Claims 1-5, 8, 10-11, and 17 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chinol et al. (1987) *J Nucl Med* 28:1465 ("Chinol") in light of Hnatowich et al. (1983) *J Immunol Meth* 65:147 ("Hnatowich"). Chinol describes preparation of ^{90}Yttrium-labeled antibodies using methods according to Hnatowich. The Examiner states that HPLC steps conducted after labeling were for the purpose of analyzing radiochemical purity (citing the paragraph of Chinol spanning pages 1469-1470), and that purification is therefore not a prerequisite to *in vivo* use. Office Action, at page 5, ¶ 2-5.

As in Mather, the radiolabeling methods of Chinol yield antibodies having only modest specific activity (1-3 mCi/mg), which are therefore largely inadequate for clinical use. Claim 1 is amended to recite a radiolabeled protein, ligand or peptide "having a specific

activity of at least about 5 mCi/mg." Support for the claim amendment can be found in the subject application as originally filed, for example at page 13, line 11, through page 14, line 1 and in original claim 19 (now canceled). Based thereon, claim 1 is believed to be patentably distinguished over Chinol. Claims 2-5, 8, 10-11, and 17 ultimately depend from claim 1 and are also believed to be patentably distinguished over Chinol. Thus, applicant respectfully requests that the rejection of claims 1-5, 8, 10-11, and 17 under 35 U.S.C. § 102(b) based on Chinol be withdrawn. Allowance of claims 1-5, 8, 10-11, and 17 is also respectfully requested.

Rejection of Claims Under 35 U.S.C. §§ 102(b) and 102(e)
Based on U.S. Patent No. 5,942,210

Claims 1-3, 5, 17 and 19 are rejected under 35 U.S.C. § 102(b) or § 102(e) as allegedly anticipated by U.S. Patent No. 5,942,210 ("the '210 patent," also PCT International Publication No. WO 96/14879). In particular, the Examiner contends that the '210 patent teaches preparation of antibodies labeled with a therapeutic radioisotope. Office Action, at page 5, ¶ 6 through page 6, ¶ 5. Applicant respectfully traverses this rejection as follows.

The '210 patent describes a "one-pot" method for radiolabeling that involves labeling of a lyophilized conjugate/transchelator/reducing agent mixture via addition of a solution containing the isotope. ^{99}Tc-labeled antibodies having high specific activity were prepared using the one-pot method and administered to test animals, apparently without a prior purification step. The Examiner contends that the '210 patent also teaches preparation of therapeutic radioconjugates comprising rhenium. Office Action, at page 6, ¶ 2.

Applicant responds that the Examiner has erroneously interpreted the disclosure of the '210 patent. As set forth in the attached Declaration under 37 C.F.R. § 1.132, the radiolabeling methods of the '210 patent are unsuitable for preparing radiolabeled conjugates useful for therapy, *i.e.* conjugates that include high energy metallic isotopes such as ^{90}Y. Contrary to the suggestion of the Examiner, the '210 patent suggests, but does not show, preparation of therapeutic radioconjugates. Absent any supporting experimental results, a skilled artisan would find the suggested method implausible.

Claim 1 is amended to include the term "therapeutic" to describe "radioisotope" in step (i). The radiolabeling methods of the present application can be used to prepare radiolabeled proteins, ligands, or peptides having high specific activity. In contrast to the

radiolabeling methods of the '210 patent, the methods of the present disclosure include the use of a high energy metallic radioisotope, ^{90}Y, whereby the resultant radioconjugate is suitable for therapeutic administration to a subject in the absence of a purification step.

Based on the foregoing, claim 1 is believed to be patentably distinguished over the '210 patent (Ultee). Claims 2-5, 8, 10-11, and 17 ultimately depend from claim 1 and are also believed to be patentably distinguished over the '210 patent. Thus, applicant respectfully requests that the rejection of claims 1-3, 5, 17 and 19 under 35 U.S.C. § 102(b) and/or 102(e) based on the '210 patent be withdrawn. Allowance of claims 3, 5, 17 and 19 is also respectfully requested.

Response to Notice of Draftsperson's Patent Drawing Review

The Draftsperson has objected under 37 C.F.R. § 1.84(e) to copy machine marks on Figure 1. A substitute Figure 1 is submitted herewith, which is believed to correct the noted defect.

Conclusion

All objections and rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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Enclosures: Appendix
§ 1.132 Affidavit of Paul Chinn

APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at page 14, line 3, is amended as follows. Deleted text is included in brackets ([ ]) and added text is underlined.

Copending applications 09/[ ]259,337 and 09/[ ]259,347, co-owned and submitted concurrently herewith, disclose binding assays which may be used to assess the percent binding affinity and immunoreactivity of conjugates after labeling if desirable. It should be stressed that, although no further purification is required after the labeling methods of the present invention, a TLC-based assay to verify the level of radioincorporation should always be performed so as not to jeopardize the health of the patient. Such an assay can be performed in about 3-4 minutes, and should not significantly affect the stability or efficacy of the radiotherapeutic.

IN THE CLAIMS:

The claims were amended as indicated below. Deleted text is included in brackets ([ ]) and added text is underlined.

1. (Amended) A method for radiolabeling a chelator-conjugated protein, ligand or peptide with a therapeutic radioisotope for administration to a patient comprising

(i) mixing the chelator-conjugated protein, ligand or peptide with a solution comprising the therapeutic radioisotope or salt thereof, and

(ii) incubating the mixture for a sufficient amount of time under amiable conditions such that a radiolabeled protein, ligand or peptide having sufficient purity[, specific activity] and binding specificity, and having a specific activity of at least about 5 mCi/mg, and is achieved such that the radiolabeled [antibody] protein, ligand or peptide may be administered directly to the patient without further purification.